

NEUROBLASTOMA SYMPATHICUM: REPORT OF ONE CASE.¹

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SINCE the publication, in 1910, of Wright's² article on neuroblastoma, the recognition of tumors of sympathetic nerve-cell origin has been more frequent, and several additional cases have been described. The case herein reported is an example of this type of tumor in which clinical diagnosis was confirmed by post-mortem examination.

Case 257376, a boy, aged thirteen years, came to the Mayo Clinic January 1, 1919, for the relief of failing vision, weakness and "small lumps" in the scalp. One other child in the family had "multiple necroses of the skull." The mother had had four miscarriages. The patient had had croup at four and pertussis at six; his tonsils and adenoids had been removed four years before. He was in the eighth grade at school. Six months before examination the parents had noticed small lumps in his scalp, pallor and loss of strength. The local physician examined the eye-grounds and reported choked disks; he prescribed potassium iodide in small doses. Loss of strength and vision had been progressive and the tumors in the scalp had doubled in size. For a month there had been intervals of pain in the knees and hips. There had been scarcely any headache and no vomiting. Sphincter control had always been normal. He had never suffered hemorrhage from the mucous surfaces nor any skin rashes, and there was no history of gastro-intestinal or genito-urinary disturbance.

The examination revealed a well-developed boy, moderately emaciated, whose skin was very pale, with a slight greenish tint. The entire forehead and vertex were nodular, with tumors varying in diameter from 2 cm. to 6 cm. Some of the nodules were rather soft, others quite hard. They were not movable and apparently were attached to the cranial bones. The site of the anterior fontanelle was sunken and the cranial sutures generally were separated. The superficial veins of the scalp were greatly dilated. Moderate bilateral exophthalmos was present in almost equal degree. The cervical glands on both sides were only slightly enlarged, but were very hard. Tenderness was extreme on firm pressure over the sternum and along the course of the ribs. A smooth liver edge was palpable on deep inspiration and a smooth mass was also felt in the left hypochondrium; this mass, which descended on inspiration, was suggestive of the spleen, although a

¹ Presented for publication, March 24, 1920.

² Neurocytoma or neuroblastoma, a kind of tumor not generally recognized, Jour. Exper. Med., 1916, xii, 556-561.

notched border was not distinct. Careful palpation of the left flank several times by different examiners gave no suggestion of a retroperitoneal mass. The right testicle was undescended.

The breath sounds were clear over both lungs. The heart-rate was rapid, and the pulmonic second sound was accentuated rather markedly. The rhythm was regular, but there was a blowing systolic murmur at the base of the heart, not transmitted.

Ophthalmological examination revealed bilateral choked disk of two diopters. A detailed neurological examination yielded negative results.

The urine contained nothing significant; Bence-Jones's protein was absent. The hemoglobin (Dare) was 30 per cent.; the erythrocytes were 1,580,000 and the leukocytes 6200; the differential blood count was normal and the blood-Wassermann reaction on both the patient and the father were negative.



FIG. 1.—Roentgenologic appearance of metastatic tumor in the skull bones.

In the roentgenogram of the skull there was evidence of a diffuse porosity suggesting the osteoclastic type of bone-malignancy (Fig. 1). Papules and some scarring about the body were noted. In view of this and the roentgenological finding, the familial history of miscarriages, some suggestive scarring about the uvula and fauces, and slight roughening of the tibiae, Dr. Stokes considered the possibility of hereditary syphilis. Because of the tumor in the left hypochondrium, the anemia, the cranial tumors, the exophthalmos and the roentgen-ray findings I had suggested a diagnosis of neuroblastoma sympathicum, probably primary in the left

adrenal. This condition, however, is too rare for positive diagnostic conviction, and antiluetic therapy was instituted.

For four days after the patient was admitted to the clinic the temperature ranged from 100° to 102° F., but then returned to normal, and remained so. The pulse-rate varied from 90 to 150. At intervals there was much pain in the knees and in the back. The child's condition remained essentially the same for two months; he then died.

The postmortem examination was conducted by Dr. W. W. Bissell, and the following pertinent lesions were named in the anatomic diagnosis:

"Large malignant hypernephroma (?); of the left adrenal; multiple extensive hypernephroma (?) metastases to the bones of the skull, the sternum, vertebrae, ribs and to the lateral lumbar and retro-aortic lymph nodes; very extensive tumor rarefaction and softening of the skull bones; very extensive tumor pressure molding of the brain; very marked bulging (pressure exophthalmos) of both eyes; marked bilateral disseminated hypostatic bronchopneumonia; moderate catarrhal tracheobronchitis; marked hyperplasia and hyperemia of the spleen; slight hyperplasia of the tracheobronchial lymph nodes."

Abstracts from the protocol are as follows:

"This is the body of a very well-developed, but very poorly nourished young white boy, apparently in the neighborhood of fourteen years of age. There are numerous nodules in the tissue of the scalp which, to the feel, are attached to the bone and vary in size from less than 1 cm. to 5 or 6 cm. in diameter. It is noteworthy that the head is considerably enlarged, being broadened in the temporal diameter. The root of the nose is greatly broadened. The distance between the pupils has the appearance of having been widened. There is no squint, but the eyes are protruding. In either upper lid, but more particularly in the left, there is a black-and-blue discoloration, as if this exophthalmos were, so to speak, 'acute.'

"In placing the body on the table perfectly straight, it is distinctly observed that the left flank is slightly more rounded than the right, the fulness being more marked just below the costal arch. No distinct mass, however, can be felt in the left flank. The skin of the body generally is quite pale. There is a very slight edema in the subcutaneous tissues about the ankles. The sternal end of the right clavicle is quite prominent and the skin over this particular area is somewhat tighter than the skin elsewhere on the body, for example, over the ribs.

"On opening the body through a midline, ventral incision, a considerably enlarged spleen presents beneath the costal arch; to the feel this is the spleen of hyperplasia. A larger mass beneath the spleen and pancreas fills the left upper abdominal quadrant.

It is fist-sized, of irregular shape and nodular, and is attached to or in close relation with the upper pole of the left kidney. This tumor mass is entirely retroperitoneal. It is a tumor of the left adrenal gland, and in no sense involves the kidney. Some of the nodules on its surface, particularly those of light pink color, are quite firm, while others of deep red color are slightly fluctuant. On surfaces made by sectioning the light salmon-pink nodules are of the consistency of brain tissue, while the deep red ones are gelatinous, easily destroyed by pressure and ooze blood freely. This tumor has originated from the left adrenal gland. It is directly continuous with it, and only a very small remnant of adrenal cortex remains intact, a small ear of the upper pole.

"The retroperitoneal and lateral lumbar lymph nodes are the seat of a neoplastic infiltration; an infiltration with tumor substance of the consistency and color of the adrenal tumor. In the lumbodorsal vertebral column there is a very extensive involvement of the bodies of the vertebræ together with their arches; an involvement entirely similar to that noted below in the skull.

"Just over the sternal end of the left clavicle, where the skin is somewhat tight, there is a small lymph node which is the seat of tumor metastasis. The ribs and sternum are the seat of many very early hemorrhagic tumor metastases, most of which have not yet broken through the medullary portion of the bone.

"The nodules in the scalp are tense, some of them slightly fluctuant; others more markedly so. On reflecting the scalp these nodules are found to be beneath the pericranium. They are very firmly attached to it, and it is with great difficulty that the scalp tissues are reflected without more or less destruction of these nodules. These tumors take origin in the medullary portion of the bone; the outer table of bone is honey-combed in such a way that numerous little prickles of bony material project from the skull. The larger tumor masses are formed from a conglomeration of many small nodules (Fig. 2). The entire calvarium is very flexible in any direction of pressure. On viewing it from the inside, many variable sized tumor masses, covered by dura, bulge inward toward the brain (Fig. 3). These are deep chocolate to light yellow in color. On opening some of these thicker tumor masses in the temporal regions they present areas of deep red hemorrhage; in other places the appearance suggests that of brain tissue, yellow to salmon-pink in color. In four places these extradural tumors have perforated the dura, but have remained slightly encapsulated, not involving the leptomeninges. The largest of the tumor masses from the inner surface of the skull measures 5 cm. by 4 cm. by 2.5 cm.

"Wherever the tumor has bulged into the cranial cavity there is a corresponding facet or depression in the brain itself. The brain is molded into an irregular, lobated organ (Fig. 4). In the right

temporoparietal region appears the largest molding, a cup measuring 4 cm. in diameter and 2 cm. in depth. In the base of the



FIG. 2.—Outer surface of the calvarium.



FIG. 3.—Inner surface of the calvarium.

skull there are only a few of these metastases, the largest arising in the right anterior fossa and bulging into the right orbit rather than into the cranial cavity.



FIG. 4.—The superior aspect of the brain; marked pressure molding apparent.



FIG. 5.—Metastatic tumor in a lymph node. $\times 100$.

"There are no metastases to be found in any of the parenchymatous organs—they are confined to the osseous and lymphatic tissues."

In microscopic specimens of the adrenal tumor proper, as well as in those taken from blocks of the metastatic nodules (Fig. 5), none of the characteristics of hypernephroma were found. Areas

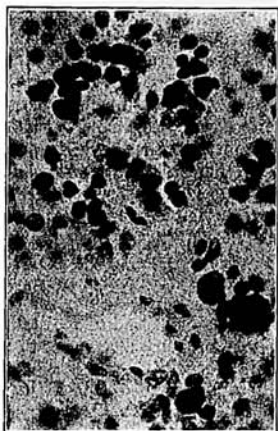


FIG. 6.—Great variation in the size and form of tumor cells; rosette in the center of the field. $\times 500$.

of recent hemorrhage occurred throughout. The tumor cells were arranged indiscriminately, rather closely packed in some places

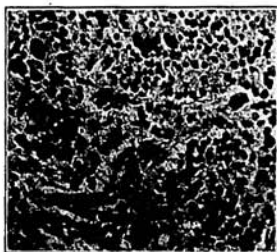


FIG. 7.—Two primitive ganglia in the field. Many tumor giant cells with one foreign body giant cell near the top of the field.

with very little connective-tissue stroma. In other areas a considerable amount of young fibrous tissue widely separated the aggregates of tumor cells. The tumor cells varied in size (Fig. 6),

the nuclei of the greater number approximated the size of a small lymphocyte; the predominant shape was oval. The chromatin was evenly spread through the nucleus and stained rather deeply. In the larger cell forms, which in places were twice the size of a small lymphocyte, the nuclear outline was very irregular; the chromatin in discrete granules and a well-marked nucleolus were present. These larger forms did not stain so deeply as the smaller ones. Rosette formation was present, but not uniformly throughout the tissue (Fig. 7). In a few places were bundles of very fine fibrils in association with clumps of tumor cells, presenting the appearance of primitive sympathetic ganglia (Fig. 6). There were many true tumor giant cells, with an occasional foreign body giant cell (Fig. 6); mitotic figures were numerous. A piece of tissue removed from the left adrenal contained a bit of normal cortex; the medulla, however, was entirely replaced by tumor tissue.

With these observations a diagnosis of neuroblastoma sympathicum was established. Grossly the striking similarity of this tissue to that of hypernephroma might lead to a mistaken gross diagnosis were it not for the extraordinary metastases to bone, particularly to bones of the skull.³

INFLUENZA IN THE TUBERCULOUS.

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DURING the recent pandemic of influenza we have been struck by several paradoxical phenomena in the etiology and clinical course of tuberculosis of the lung. There is ample and reliable evidence that nearly everyone living in a modern city has been infected with tubercle bacilli at some period of his life, usually before he has reached adolescence. It appears that this infection is effective in producing pathological changes in the lung and pleura, but that these morbid changes remain latent in the vast majority of cases. Attempts to explain the reason why in some persons tubercle bacilli produce disease and perhaps death, while in others they remain within the body merely as harmless invaders, have suggested the importance of a "predisposition" which varies with the individual. Among the factors which reduce the resisting powers or enhance

³ Dr. J. H. Wright, of the Harvard Medical School, also examined specimens from the tumor and verified the diagnosis.

predisposition, influenza or the microorganism responsible for it has been considered as one of the most effective. Similarly the undulating course of chronic pulmonary tuberculosis has been explained as due mainly to mixed infections, especially to streptococci and to the Pfeiffer bacillus, which often are found in abundance in the sputum of tuberculous patients. It has been claimed that patients who are so fortunate as to escape superinfection with the secondary invaders do well, while those who are thus infected run a more or less stormy course, ending finally in death.

In a previous communication on this subject¹ it was shown that during the epidemic of 1918-19 influenza could be exonerated from the charge of playing an important role in the etiology of tuberculosis and in affecting its clinical course. Nowhere has there been observed an increase in the morbidity and mortality from tuberculosis soon after the subsidence of the epidemic. Clinical observation revealed the astonishing fact that tuberculous patients stood the acute epidemic disease quite well; it appeared that the proportion of fatal cases was not greater but apparently even smaller than among the non-tuberculous. This fact has so far been confirmed by most writers on this subject, who have based their assertions on observations of large numbers of cases. Thus F. H. Gerwiener² had similar experiences in a Hungarian military sanatorium of 2400 beds. The epidemic was raging in the city and in the suburban villages, and no precautions were taken to keep the plague out of the institution or to isolate the patients. Yet very few cases occurred among the tuberculous patients in the sanatorium. It is, however, noteworthy that among the healthy personnel of the sanatorium, the physicians, nurses, orderlies, numerous and severe cases of influenza were observed. Similarly, Bochall³ observed that tuberculosis created a certain degree of immunity against influenza, and that, when tuberculous patients are affected, the prognosis is much better than in non-tuberculous individuals. Wurtzen,⁴ comparing the morbidity and mortality from influenzal pneumonia among tuberculous patients with that in previously healthy individuals, found that the chances of contracting pneumonia are about the same in both groups. However, while 36 per cent. of previously healthy soldiers succumbed to influenzal pneumonia, 83 per cent. of those who were tuberculous died. In France, Weil reports from the services of Léon Bernard and Rist, at the Laennec Hospital, that two wards filled with 50 civil tuberculous patients were completely spared during the influenza epidemic; that in four wards with 105 military patients only 3 cases of in-

¹ Fishberg, M.: Influenza and Tuberculosis, *Am. Rev. Tuberc.*, 1919, iii, 532.

² Die pandemische Grippe in ihren Beziehungen und Folgeerscheinungen zur Lungentuberkulose, *Beit. z. Klin. d. Tuberkulose*, 1919, xlii, 33.

³ München. med. Wchnsch., 1919, lxvi, No. 12.

⁴ Ugeskr. f. Laeger, 1919, lxxxi, 673.